cludes. The questions still to be addressed include whether cold viruses, which like other viruses have the chameleon-like ability to mutate, will evolve new tricks before the company can get its anticold compounds through lengthy trials and approval procedures. "It's a concern," McKinlay says, "but we remain optimistic."

Researchers have also been trying to block receptor binding by the AIDS virus, HIV, which latches on to a receptor molecule called CD4 on the surface of the T cells it infects. Original attempts to combat HIV infection with a soluble form of the CD4 receptor showed promise in tests on cultured cells but failed clinical trials. "It was a frustrating effort," says Ray Sweet of Smith Kline, Beecham, which made one of the compounds tested. Genentech dropped a similar effort.

Despite the frustrating results with soluble CD4, however, researchers haven't given up on finding a compound that can block HIV binding to cells. About 3 years ago, teams led by Howard Hughes Medical Institute researchers Stephen Harrison at Harvard and Wayne Hendrickson at Columbia performed x-ray crystallographic studies of a CD4 receptor fragment. Their results suggested CD4 makes contact with a viral glycoprotein resting in a groove on the HIV surface. The area of contact is about 25 Ångstroms by 12 Ångstroms, small enough that it might be possible to prevent binding with a small CD4 mimic that attaches to HIV, says Harrison.

Conversely, it might be possible to block the binding with small molecules targeted to CD4 itself. That approach could have an advantage, says James Jenson, a vice president at the startup firm Procept Inc. of Cambridge, Massachusetts, one of several companies looking for ways to block HIV binding to cells. He notes that existing AIDS drugs, such as AZT, target proteins associated with HIV, which mutate rapidly, making the virus drug-resistant. The human CD4 protein may be less subject to mutation and therefore a better target. Later this year, Procept plans to file an investigative new drug application with the Food and Drug Administration for one of its drugs, a small molecule custom-designed to block HIV binding to CD4.

Procept is only one of many drug companies where there's a pervasive new sense of looking back to forge the future. In that process, they're reinvigorating the venerable scientific specialty of synthetic chemistry. Synthetic chemists, who were once at the hub of drug development and whose contributions were recently spurned by a brash young generation of molecular biologists, are now regaining their stature as essential members of the drug development team. And molecular biologists are learning that synthesis is not just a way of producing drugs, but is also a collaborative means of doing top science.

–Anne Simon Moffat

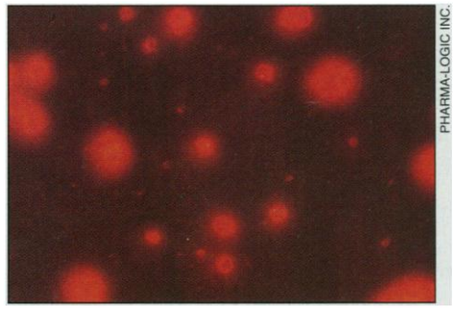
DRUG DELIVERY

Stand and Deliver: Getting Peptide Drugs Into the Body

Beginning with recombinant human insulin, which went on the market in 1982, the biotech industry has produced a wide range of potentially life-saving new drugs. But in the pharmaceutical world, making a new drug is only half the battle. Once a drug has been developed, researchers face the challenge of figuring out how to get it into the body in doses high enough to do the job, but not so high as to poison healthy tissues and cells.

That's been a major hurdle for the biotech industry, since almost all of its products to date are large peptides or proteins. And proteins, because they are rapidly broken down by digestive enzymes and don't pass readily through the skin, can only be administered by costly, inconvenient, and painful injections. No wonder drug delivery is seen as a bottleneck by insiders like Russ Potts, director of research sciences at the biotech company Cygnus Therapeutic Systems in Redwood City, California: "Drug delivery represents the potential Achilles' heel of biotechnology's peptide drug industry."

The industry isn't backing down from the challenge. On the contrary, it is fighting to devise alternate methods for delivery of peptide and protein drugs. "Every major pharmaceutical company [has] at least an in-house pilot peptide drug delivery program; if not, they contract out to companies specializing in drug delivery," says Charlie White, director of marketing at Medisorb Technologies International, a Cincinnati-based company that performs such drug delivery research. Although it's too early to say when efforts to make peptide drugs available in noninjectable forms will pay off, Gordon Amidon, professor of pharmaceutics at the University of Michigan, Ann Arbor, says it's a good sign that "drug delivery has gained equal footing with drug discovery in the pharmaceutical world."



PHARMA-LOGIC INC.

Small world. Microcrystals of submicron size (the smallest here is 0.5 micron) might be used to deliver some peptide drugs.

Such "equal footing" is reflected by the enormous research activity now exploring several strategies for resolving the peptide delivery dilemma. Among them, three stand out as promising: Researchers are trying to develop body-friendly microspheres for oral delivery that will protect these fragile molecules en route to a desirable absorption site in the intestines; they are experimenting with ways to aerosolize them for inhalation and absorption through the lungs; and they are designing skin patches that use electric currents to drive proteins into the skin and the blood circulation.

Oral delivery: making peptides palatable

Oral delivery is a tantalizing double-edged sword for the biotech industry. On the one hand, it's the most desirable route for getting drugs into the body, because it's so convenient. Yet the oral route is also the most hazardous to the health of the peptides and proteins themselves, and probably will be the most difficult to achieve. In fact, "a decade ago oral peptide delivery was considered fantasy," notes pharmaceutical scientist Vincent Lee of the University of Southern California. And even today, though companies are plunging into the area, their early efforts have generated as much skepticism as excitement.

The problem is that proteins can't be taken in ordinary pills or capsules because their protective coatings break down in the stomach, exposing their contents to protein-splitting enzymes before they can be absorbed into the bloodstream. The trick, then, is to find a way to camouflage peptides and proteins long enough to slip them past the digestive enzymes to the intestinal lining, where chances for absorption are greatest.

Several companies think they can pull off that trick by protecting proteins from digestive enzymes by encapsulating them in microspheres—tiny particles, ranging in size from 50 nanometers up to 20 microns, made with any of a variety of inert materials, including synthetic and natural polymers. For example, InnoVet Inc., in West Palm Beach, Florida, working with Matrix Bioscience in Research Triangle Park, North Carolina, is experimenting with a natural fatty acid "biopolymer" to administer insulin orally; they say that they have had some success in rodents. Alkermes Inc., in Cambridge, Massachusetts, is using the corn protein zein to deliver its peptides. And, as offbeat entries, there are the "proteinoids,"

SOURCE: CYGNUS THERAPEUTIC SYSTEMS ILLUSTRATION: TRACY KEATON

groups of unusual branched polymers, made entirely of amino acids. Emisphere Technologies, which holds the worldwide core patent on proteinoid technology, is experimenting with these unusual polymers as peptide-protecting microspheres.

Lots of people are skeptical about how well the microspheres will ever work. The mechanisms by which they might deliver peptides through the intestinal lining are not well understood, and so far, in animal studies, generally less than 10% and typically less than 5% of the administered dose gets into blood. Nonetheless, some big players are hovering around the microsphere experiments, willing to risk significant R&D dollars on the outcome. Emisphere Technologies, for example, is working with Upjohn, Sandoz, and Schering-Plough, who are all extremely eager to make their peptide products available as noninjectables.

Respiratory delivery: a whiff of the future

Although much research is aimed at making it possible for people to take peptide drugs by mouth, the intestinal lining is not the only possible port of entry. In fact, the lining of the lungs has characteristics that make it just about ideal for absorbing peptides and proteins, says Peter Byron, an expert on aerosol drug delivery at the Medical College of Virginia in Richmond. If aerosolized drugs can be introduced deeply enough into the lungs, they can reach the bloodstream quickly and easily, since they need penetrate only a thin layer of epithelium before entering the rich capillary beds beneath. Furthermore, proteins are in less danger of being destroyed in the lungs than in the digestive tract, because the lungs contain inhibitors that keep protein-splitting enzymes in check.

Several companies are designing delivery systems that exploit these advantages of the lungs as a road to the body. Most have adopted the strategy of dissolving a protein in a water or salt solution and administering it in a nasal spray or a nebulizer (which aerosolizes the peptide for inhalation by mouth). One of the earliest fruits of this approach could be a new therapy for cystic fibrosis (CF). That therapy, a nebulized form of the enzyme DNase that helps break down the thick mucous clogging CF patients' lungs, is perhaps only 12 months away from Food and Drug Administration (FDA) approval, according to the drug's developer, Genentech Inc. of South San Francisco. The company has completed a large clinical trial in humans and filed a product licensing application with FDA. Sandoz has also submitted an application to FDA for a nasal spray form of calcitonin, a small peptide hormone being tested for the treatment of osteoporosis.

But in the peptide drug delivery field no approach is totally without complications, and while the CF and other efforts are enjoying some success, proteins in solution have the drawback that they tend to break down rapidly. What is more, bacterial contamination is a frequent problem. One company, Inhale Therapeutic Systems of Palo Alto, California, is trying to circumvent these problems by aerosolizing peptides and proteins from a powder formulation. Proteins administered as a powder aerosol can enter the circulation quite efficiently through the deep lungs, says John Patton, the company's cofounder and vice president for research. In animal studies, approximately 55% to 60% of the aerosolized cytokines alpha interferon and granulocyte colony stimulating factor were absorbed through the lung epithelium and taken up by the bloodstream.

Moving in. Iontophoresis *(above)* forces proteins through the skin's hair follicles and sweat glands, while electroporation *(lower diagram)* opens additional pores.

Transdermal delivery: electrifying feats

The lungs and the intestines are readily exploitable routes into the body—but so is the skin. That's already been shown by transdermal patches that have proved to be an extremely convenient and efficient way to administer drugs including nitroglycerin for angina and estrogen for hormonal replacement therapy at menopause. That would make patches seem an attractive alternative for peptides. So far, though, patches have been virtually useless for delivering peptide drugs, which are too big and too fat-insoluble to pass through the lipid layers of the skin to the underlying blood vessels.

Because the stakes are high, however, some biotech companies are managing to find a way around this obstacle, too. By exploiting the electric charges on proteins, these molecules can be forced through the skin. One such approach, called iontophoresis or electrotransport, uses a constant, low-level electric current to move the charged molecules into the skin. By simple charge repulsion, the electric current pushes the charged protein molecules through existing pathways in the skin, such as the hair follicles and sweat glands. Iontophoresis has been around for about 100 years and was used frequently in medical practice in the 1930s and '40s for transdermal drug delivery. But only within the past 10 years has it been resurrected in the attempt to aid transdermal delivery of peptides and proteins by companies, including Alza Corp. and Elan Corp. of Athlone, Ireland.

Alza is using a disposable skin patch with built-in electronics, says Felix Theeuwes, the company's executive vice president. Depending on the peptide being administered, the patch applies three to 12 volts of electricity to the skin for anywhere from minutes to hours. The device has begun trials in humans, and though Theeuwes declines to say what peptides are being tested, he reports that patients feel no discomfort other than a tingling sensation at the patch site. Elan Corp.'s device, called Panoderm, looks something like a watch. It's a little less than an inch thick and contains a disposable drug cartridge. Like Alza, Elan has gone into clinical trials but isn't saying what peptides are being tested or when the device is likely to be available.

Iontophoresis isn't the only electrical route into the skin. A system being tried at Cygnus is based on transdermal electroporation, which uses ultra-short pulses, lasting a few milliseconds with an intensity of a few hundred volts, to induce changes in the underlying skin that will allow the drugs to pass. The technology was developed by Massachusetts Institute of Technology researchers Robert Langer and James Weaver, who hold a patent for which Cygnus is the sole licensee.

Electroporation might have a considerable advantage over the iontophoresis. Russ Potts of Cygnus says his group directly compared the efficiency of electroporation and iontophoresis in inducing transport of the small peptide leutinizing hormone releasing hormone across human skin in a lab assay. Electroporation gave a 10-fold increase in the amount of drug that passed through, sufficiently encouraging, Potts said, that studies in rodents will begin in a few months.

For proprietary reasons, researchers aren't revealing many details about this or the other drug delivery systems they're testing, so it's hard to say at this point which ones—if any—will eventually make it to market. Yet it is clear that because of the potential therapeutic benefits of many of the biotech industry's peptide and protein drugs, the stakes are high enough to draw even the conservative betters to the drug delivery window.

–Brigid M. Wallace and **Jill S. Lasker**

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